

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
US Department of Commerce  
United States Patent and Trademark  
Office, PCT  
2011 South Clark Place Room  
CP2/5C24  
Arlington, VA 22202  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 28 February 2001 (28.02.01)	
<b>International application No.</b> PCT/US99/25187	<b>Applicant's or agent's file reference</b> DC-0121
<b>International filing date (day/month/year)</b> 28 October 1999 (28.10.99)	<b>Priority date (day/month/year)</b> 07 December 1998 (07.12.98)
<b>Applicant</b> DELEO, Joyce, A. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:27 June 2000 (27.06.00)☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	<b>Authorized officer</b>  Maria Kirchner Telephone No.: (41-22) 338.83.38
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## PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING  
AMENDMENTS OF THE CLAIMS(PCT Rule 62 and  
Administrative Instructions, Section 417)

From the INTERNATIONAL BUREAU

To:

Commissioner  
US Department of Commerce  
United States Patent and Trademark  
Office, PCT  
2011 South Clark Place Room  
CP2/5C24  
Arlington, VA 22202  
ETATS-UNIS D'AMERIQUE

in its capacity as International Preliminary Examining Authority

Date of mailing (day/month/year)

28 February 2001 (28.02.01)

International application No.

PCT/US99/25187

International filing date (day/month/year)

28 October 1999 (28.10.99)

Applicant

TRUSTEES OF DARTMOUTH COLLEGE et al

The International Bureau hereby informs the International Preliminary Examining Authority that no amendments under Article 19 have been received by the International Bureau (Administrative Instructions, Section 417).

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

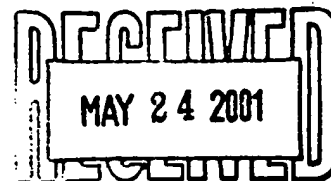
Facsimile No. (41-22) 740.14.35

Authorized officer

Maria Kirchner

Telephone No. (41-22) 338.83.38

# PATENT COOPERATION TREATY



From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:  
JANE MASSEY LICATA  
LAW OFFICES OF JANE MASSEY LICATA  
66 E. MAIN STREET  
MARLTON, NJ 08053

## PCT NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing  
(day/month/year)

21 MAY 2001

Applicant's or agent's file reference

DC-0121

### IMPORTANT NOTIFICATION

International application No.

PCT/US99/25187

International filing date (day/month/year)

28 October 1999 (28.10.1999)

Priority date (day/month/year)

07 December 1998 (07.12.1998)

Applicant

TRUSTEES OF DARTMOUTH COLLEGE

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231  
Facsimile No. (703)305-3230  
Form PCT/IPEA/416 (July 1992)

Authorized officer

Dorina A. Jagoe

Telephone No. (703) 308-0196

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:  
JANE MASSEY LICATA  
LAW OFFICES OF JANE MASSEY LICATA  
66 E. MAIN STREET  
MARLTON, NJ 08053

## PCT NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing  
(day/month/year)

21 MAY 2001

Applicant's or agent's file reference

DC-0121

### IMPORTANT NOTIFICATION

International application No.

PCT/US99/25187

International filing date (day/month/year)

28 October 1999 (28.10.1999)

Priority date (day/month/year)

07 December 1998 (07.12.1998)

Applicant

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1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

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For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231  
Facsimile No. (703)305-3230  
Form PCT/IPEA/416 (July 1992)

Authorized officer

Dorinda A. Jagoe

Telephone No. (703) 308-0196

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/25187

## I. Basis of the report

### 1. With regard to the elements of the international application:\*

- ☒ the international application as originally filed.
- ☒ the description:  
 pages 1-14 \_\_\_\_\_ as originally filed  
 pages NONE \_\_\_\_\_, filed with the demand  
 pages NONE \_\_\_\_\_, filed with the letter of \_\_\_\_\_.
- ☒ the claims:  
 pages 15 and 16 \_\_\_\_\_, as originally filed  
 pages NONE \_\_\_\_\_, as amended (together with any statement) under Article 19  
 pages NONE \_\_\_\_\_, filed with the demand  
 pages NONE \_\_\_\_\_, filed with the letter of \_\_\_\_\_.
- ☐ the drawings:  
 pages NONE \_\_\_\_\_, as originally filed  
 pages NONE \_\_\_\_\_, filed with the demand  
 pages NONE \_\_\_\_\_, filed with the letter of \_\_\_\_\_.
- ☐ the sequence listing part of the description:  
 pages NONE \_\_\_\_\_, as originally filed  
 pages NONE \_\_\_\_\_, filed with the demand  
 pages NONE \_\_\_\_\_, filed with the letter of \_\_\_\_\_.

### 2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

### 3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

### 4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

### 5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).\*\*

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

\*\* Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/25187

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.  
☒ paid additional fees.  
☐ paid additional fees under protest.  
☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention is accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.  
☒ not complied with for the following reasons:

Group I, claims 1-2, drawn to a method of preventing and reducing pain in an animal.

Group II, claims 3-7, drawn to a non-human animal model and a method for producing said non-human animal model.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature of the Group I invention is a method of preventing or reducing lower back pain in an animal by administering methotrexate, while the special technical feature of the Group II invention is the animal model and the method of making the animal model. Since the special technical feature of the Group I invention is not present in the Group II invention being claimed and the special technical feature in the Group II invention is not present in the Group I invention being claimed, unity of invention is lacking.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.  
☐ the parts relating to claims Nos. \_\_\_\_

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US99/25187

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. STATEMENT

Novelty (N)	Claims <u>3-7</u>	YES
	Claims <u>1-2</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-7</u>	NO
Industrial Applicability (IA)	Claims <u>1-7</u>	YES
	Claims <u>NONE</u>	NO

### 2. CITATIONS AND EXPLANATIONS (Rule 70.7)

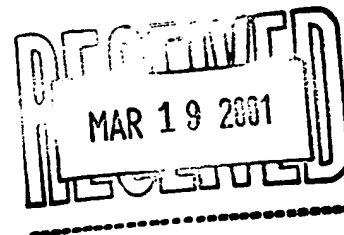
Claims 1-2 lack novelty under PCT Article 33(2) as being anticipated by Geyer et al. The claims are drawn to a method of preventing or reducing pain comprising administering methotrexate and an animal model and method of making an animal model. Geyer et al. teach administration of methotrexate to adult rats via the lateral cerebral ventricle, before irradiating the cervical spine. Methotrexate administration resulted in protection against white matter necrosis and paralysis. (see abstract)

Claims 1-7 lack an inventive step under PCT Article 33(3) as being obvious over Mori et al. The claims are drawn to a method of preventing or reducing pain comprising administering methotrexate and an animal model and method of making an animal model. Mori et al. teach administration of methotrexate to mice, rats, guinea pigs and dogs. He demonstrates that methotrexate has an analgesic effect with regard to pain response to acetic acid induces writhing in mice. It differs in that there is not a surgical method recited for inducing pain in an animal model. Although there is not surgical method, it would have been obvious to evaluate an agent for pain relief in an animal by ligating the L5 spinal root to produce pain since the above cited art induces pain in an animal to evaluate methotrexate for pain relief. The motivation to employ methotrexate for pain relief purposes arises from the clear teaching of the prior art that that methotrexate has been employed for pain relief.

Applicant's response to the Written Opinion dated 02 April 2001 has been entered and considered.

----- NEW CITATIONS -----  
NONE

# PATENT COOPERATION TREATY



From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:  
JANE MASSEY LICATA  
LAW OFFICES OF JANE MASSEY LICATA  
66 E. MAIN STREET  
MARLTON, NJ 08053

Docket System ☒  
Status Report ☒  
Docket Book ☒

4/16/01

## PCT

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing  
(day/month/year)

16 MAR 2001

Applicant's or agent's file reference

DC-0121

REPLY DUE

within 1 months/days from  
the above date of mailing

International application No.

PCT/US99/25187

International filing date (day/month/year)

28 October 1999 (28.10.1999)

Priority date (day/month/year)

07 December 1998 (07.12.1998)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 31/195 and US Cl.: 514/565

Applicant

TRUSTEES OF DARTMOUTH COLLEGE

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

**When?** See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~

**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also** For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 07 April 2001 (07.04.2001)

Name and mailing address of the IPEA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer  
Marianne Cintins

Telephone No. (703) 308-0196



# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:  
JANE MASSEY LICATA  
LAW OFFICES OF JANE MASSEY LICATA  
66 E. MAIN STREET  
MARLTON, NJ 08053

## PCT

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing (day/month/year) <span style="float: right; font-size: 1.2em;">16 MAR 2001</span>	
Applicant's or agent's file reference  DC-0121	REPLY DUE within 1 months/days from the above date of mailing
International application No. PCT/US99/25187	International filing date (day/month/year) 28 October 1999 (28.10.1999)
Priority date (day/month/year) 07 December 1998 (07.12.1998)	
International Patent Classification (IPC) or both national classification and IPC  IPC(7): A61K 31/195 and US Cl.: 514/565	
Applicant  TRUSTEES OF DARTMOUTH COLLEGE	

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:
  - I ☒ Basis of the opinion
  - II ☐ Priority
  - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☒ Lack of unity of invention
  - V ☒ Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application
3. The applicant is hereby invited to reply to this opinion.
 

**When?** See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~

**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also** For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 07 April 2001 (07.04.2001)

Name and mailing address of the IPEA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231  
Facsimile No. (703)305-3230

Authorized officer  
*Jane Budger*  
Marianne Cintins  
Telephone No. (703) 308-0196

# WRITTEN OPINION

International application No.

PCT/US99/25187

## I. Basis of the opinion

### 1. With regard to the elements of the international application:\*

- ☒ the international application as originally filed
- ☐ the description:  
 pages 1-14, as originally filed  
 pages, filed with the demand  
 pages, filed with the letter of
- ☐ the claims:  
 pages 15-16, as originally filed  
 pages, as amended (together with any statement) under Article 19  
 pages, filed with the demand  
 pages, filed with the letter of
- ☐ the drawings:  
 pages, as originally filed  
 pages, filed with the demand  
 pages, filed with the letter of
- ☐ the sequence listing part of the description:  
 pages, as originally filed  
 pages, filed with the demand  
 pages, filed with the letter of

### 2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

### 3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

### 4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/fig

### 5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."

**WRITTEN OPINION.**

International application No.

PCT/US99/25187

**IV. Lack of unity of invention**

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☒ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

- ☒ all parts.
- ☐ the parts relating to claims Nos. \_\_\_\_\_.

**WRITTEN OPINION**

International application No.  
PCT/US99/25187

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. STATEMENT**

Novelty (N)	Claims <u>NONE</u>	YES
	Claims <u>1-7</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-7</u>	NO
Industrial Applicability (IA)	Claims <u>1-7</u>	YES
	Claims <u>NONE</u>	NO

**2. CITATIONS AND EXPLANATIONS**

Claims 1-7 lack novelty under PCT Article 33(2) as being anticipated by Geyer et al. (Intl. J. Oncology, Biology, Physics, August 1988). The claims are drawn to a method of preventing or reducing pain comprising administering methotrexate and an animal model and method of making an animal model. Geyer et al. teach administration of methotrexate to adult rats via the lateral cerebral ventricle, before irradiating the cervical spine. Methotrexate administration resulted in protection against white matter necrosis and paralysis (see abstract).

Claims 1-7 lack inventive step under PCT Article 33(3) as being obvious over Mori et al. The claims are drawn to a method of preventing or reducing pain comprising administering methotrexate and an animal model and method of making an animal model. Mori et al. teach administration of methotrexate to mice, rats, guinea pigs and dogs. He demonstrates that methotrexate has an analgesic effect with regard to pain response to acetic acid induces writhing in mice. It differs in that there is not a surgical method recited for inducing pain in an animal model. Although there is no surgical method, it would have been obvious to evaluate an agent for pain relief in an animal by ligating the L5 spinal root to produce pain since the above cited art induces pain in an animal to evaluate methotrexate for pain relief. The motivation to employ methotrexate for pain relief purposes arises from three clear teachings of the prior art that methotrexate has been employed for pain relief.

WRITTEN OPINION

International application No.  
PCT/US99/25187

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

**Continuation of Certain Documents Cited**

**1. Certain published documents (Rule 70.10)**

**Application No**

**Publication Date**

**Filing Date**

**Priority date (valid claim)**

Patent No.

(day/month/year)

(day/month/year)

(day/month/year)

None

None

None

None

**2. Non-written disclosures (Rule 70.9)**

Kind of non-written disclosure

Date of non-written disclosure

Date of written disclosure referring to  
non-written disclosure

(day/month/year)

(day/month/year)

None

None

None

WRITTEN OPINION

International application No.  
PCT/US99/25187

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

**TIME LIMIT:**

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

**ATTACHMENT TO CHAPTER II PCT TELEPHONE MEMORANDUM  
FOR  
LACK OF UNITY OF INVENTION**

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**Detailed Reasons For Holding Lack of Unity of Invention:**

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature of the Group I invention is a method of preventing or reducing lower back pain in an animal by administering methotrexate, while the special technical feature of the Group II invention is the animal model and the method of making the animal model. Since the special technical feature of the Group I invention is not present in the Group II invention being claimed and the special technical feature in the Group II invention is not present in the Group I invention being claimed, unity of invention is lacking.

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*Note: A copy of this form must be attached to the Opinion/Fin I R port.*

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>A61K 31/195</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 00/33830</b> <b>(43) International Publication Date:</b> 15 June 2000 (15.06.00)
<b>(21) International Application Number:</b> PCT/US99/25187 <b>(22) International Filing Date:</b> 28 October 1999 (28.10.99)  <b>(30) Priority Data:</b> 60/111,181 7 December 1998 (07.12.98) US 60/147,442 5 August 1999 (05.08.99) US  <b>(71) Applicant (for all designated States except US):</b> TRUSTEES OF DARTMOUTH COLLEGE [US/US]; Technology Transfer Office, 11 Rope Ferry Road, Hanover, NH 03755-1404 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> <u>DELEO</u> , Joyce, A. [US/US]; 38 Wellington Circle, Lebanon, NH 03766 (US). <u>WEINSTEIN</u> , James, N. [US/US]; 206 Brook Hollow, Hanover, NH 03755 (US).  <b>(74) Agents:</b> LICATA, Jane, Massey et al.; Law Offices of Jane Massey Licata, 66 E. Main Street, Marlton, NJ 08053 (US).		<b>(81) Designated States:</b> CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> AN ANIMAL MODEL AND COMPOUNDS IDENTIFIED VIA THIS MODEL FOR TREATMENT OF CHRONIC PAIN  <b>(57) Abstract</b>  An animal model for chronic pain, and in particular lower back pain, is provided. Methods of identifying agents and reducing chronic pain with identified agents such as methotrexate are also provided.		



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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/25187

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A61K 31/195

US CL : 514/565

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/565

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database BIOSIS on STN, AN 1997:162322. MORI, M. et al. 'General Pharmacological Studies of Methotrexate and 7-hydroxymethotrexate'. Oyo Yakuri (1996) Vol 52, No. 6, pages 459-470, see abstract.	1-7
X	GEYER, J.R. et al. Radiation, Methotrexate, and White Matter Necrosis: Laboratory Evidence for Neural Radioprotection with Preirradiation Methotrexate. Int. J. Radiation Oncology, Biology, Physics, August 1988, Vol. 15, No. 2, pages 373-375, see abstract	1-7

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

09 MARCH 2000

Date of mailing of the international search report

14 APR 2000

 Name and mailing address of the ISA/US  
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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/25187

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P ---- A,P	Database HCAPLUS on STN, AN 2000:29517. GOLDENBERG, M.M. 'Leflunomide, a Novel Immunomodulator for the Treatment of Active Rheumatoid Arthritis. Clin. Ther. 1999, Vol. 21, No. 11, pages 1837-1852, see abstract.	1-3 ---- 4-7

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/25187

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/25187

### B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

STN, BIOSIS, MEDLINE, CA, HCAPLUS, Methotrexate or amethopterin, model, pain, analges, animal, rat, mice or mouse, rodent, muridae, caviidae, spin?, lumb?, allodyn or gait or movement or locomotion or motor,

### BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This International Preliminary Examining Authority has found 2 inventions claimed in the International Application covered by the claims indicated below:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-2, drawn to a method of preventing and reducing pain in an animal.

Group II, claim(s) 3-7, drawn to a non-human animal model and a method for producing said non-human animal model.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature of the Group I invention is a method of preventing or reducing lower back pain in an animal by administering methotrexate while the special technical feature of the Group II invention is the animal model and the method of making the animal model. Since the special technical feature of the Group I invention is not present in the Group II invention being claimed and the special technical feature of the Group II invention is not present in the Group I invention being claimed, unity of invention is lacking.